UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/586,072	07/14/2006	Douglas E. Brough	253625	7914

23460 7590 07/20/2010

LEYDIG VOIT & MAYER, LTD
TWO PRUDENTIAL PLAZA, SUITE 4900
180 NORTH STETSON AVENUE
CHICAGO, IL 60601-6731

EXAMINER
SHEN, WU CHENG WINSTON

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
07/20/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Chgpatent@leydig.com

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/586,072	**Applicant(s)** BROUGH, DOUGLAS E.	
	Examiner WU-CHENG Winston SHEN	**Art Unit** 1632	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 24 June 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *35,39-42,45-48,52 and 53*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Continuation of 11. does NOT place the application in condition for allowance because:

(i) Applicant's arguments have failed to overcome the rejection of claims 35, 39, and 40 rejected under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005) in view of Falck-Pedersen et al. (US patent 5,837,511, issued Nov. 17, 1998; this reference is listed as reference #AJ in the IDS filed on 11/16/2006), Bout et al. (US patent 6,913,922, issued on 07/05/2005, filed on 05/18/2000) and Wigand et al. (Wigand et al., New human adenovirus (candidate adenovirus 36), a novel member of subgroup D, Arch Virol. 64(3):225-33, 1980). Applicant's arguments filed 06/24/2010 have been fully considered and they are not persuasive. Previous rejection is maintained for the reasons of record advanced on pages 4-13 of the office action mailed on 03/24/2010.

(ii) Applicant's arguments have failed to overcome the rejection of claims 41 and 42 rejected under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005), in view of in view of Falck-Pedersen et al. (US patent 5,837,511, issued Nov. 17, 1998; this reference is listed as reference #AJ in the IDS filed on 11/16/2006), Bout et al. (US patent 6,913,922, issued on 07/05/2005) and Wigand et al. (Wigand et al., New human adenovirus (candidate adenovirus 36), a novel member of subgroup D, Arch Virol. 64(3):225-33, 1980) as applied to claims 35, 39, and 40 above, and further in view of Kovesdi et al. (US patent 6,821,775, issue date, Nov. 23, 2004). Applicant's arguments filed 06/24/2010 have been fully considered and they are not persuasive. Previous rejection is maintained for the reasons of record advanced on pages 13-16 of the office action mailed on 03/24/2010.

(iii) Applicant's arguments have failed to overcome the rejection of claims 45-48 rejected under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005) in view of Falck-Pedersen et al. (US patent 5,837,511, issued Nov. 17, 1998; this reference is listed as reference #AJ in the IDS filed on 11/16/2006), Bout et al. (US patent 6,913,922, issued on 07/05/2005) and Wigand et al. (Wigand et al., New human adenovirus (candidate adenovirus 36), a novel member of subgroup D, Arch Virol. 64(3):225-33, 1980) as applied to claims 35, 39, and 40 above, and further in view of Staecker et al. (Staecker et al., Brain-derived neurotrophic factor gene therapy prevents spiral ganglion degeneration after hair cell loss. Otolaryngol Head Neck Surg. 119(1): 7-13, 1998; listed as reference EU on the IDS filed by Applicant on 11/16/2006). Applicant's arguments filed 06/24/2010 have been fully considered and they are not persuasive. Previous rejection is maintained for the reasons of record advanced on pages 16-18 of the office action mailed on 03/24/2010.

(iv) Applicant's arguments have failed to overcome the rejection of claims 52 and 53 rejected under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005) in view of Falck-Pedersen et al. (US patent 5,837,511, issued Nov. 17, 1998; this reference is listed as reference #AJ in the IDS filed on 11/16/2006), Bout et al. (US patent 6,913,922, issued on 07/05/2005) and Wigand et al. (Wigand et al., New human adenovirus (candidate adenovirus 36), a novel member of subgroup D, Arch Virol. 64(3):225-33, 1980) as applied to claims 35, 39, and 40 above, and further in view of Wickham et al. (Wickham et al., US 6,455,314, issued 09/24/2002; This patent is listed as reference BM on the IDS filed by Applicant on 11/16/2006) and Mizuguchi et al. (Mizuguchi et al., CAR- or alphav integrin-binding ablated adenovirus vectors, but not fiber-modified vectors containing RGD peptide, do not change the systemic gene transfer properties in mice, Gene Ther. 9(12):769-76, 2002). Applicant's arguments filed 06/24/2010 have been fully considered and they are not persuasive. Previous rejection is maintained for the reasons of record advanced on pages 18-20 of the office action mailed on 03/24/2010.

For the maintained 103 rejections (i) to (iv) listed above, Applicant's arguments are collectively addressed below.

Applicant argues that contrary to the assertions of the Office Action, one of ordinary skill in the art would not have had a credible reason to choose Ad28 for use in the context of a method such as described by the Zoghbi patent with a reasonable expectation of success based on the disclosure of the Wigand reference. In this regard, while the Wigand reference discloses that the genomes of Ad36 and Ad28 are similar, the Wigand reference also states that Ad36 is genetically similar to other subgroup D adenoviruses. There is nothing in the Wigand reference that would have provided a reason for one of ordinary skill in the art to have specifically selected Ad28 from among the more than 20 serotypes within of subgroup D, much less from among the 51 adenoviral serotypes known in the art (See page 4 of Applicant remarks filed on 06/24/2010).

Applicant argues that selecting an adenovirus of a specific serotype from a given subgroup is not simply a matter of "routine optimization," as alleged in the Office Action. According to M.P.E.P. § 2144.05, "differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical" (emphasis added). M.P.E.P. § 2144.05 further states that "a prima facie case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties" (emphasis added). The selection of a distinct organism (i.e., an adenovirus of a particular serotype) from among a group of related but different organisms (i.e., an adenovirus subgroup) is much different than the routine adjustment of the conditions of a particular chemical reaction or process (See page 4 of Applicant remarks filed on 06/24/2010).

Applicant argues that whether a non-group C adenovector is more or less likely to trigger a host immune response is entirely irrelevant to the unexpected properties described in the previously filed Rule 132 declaration. The prior Rule 132 declaration teaches that one of ordinary skill in the art would not have expected a non-subgroup C vector to transduce inner ear cells more efficiently than subgroup C vectors simply because the non-subgroup C vector is not of subgroup C. Thus, the claimed vector, indeed, has unexpected properties (transduction efficiency) relative to Ads vectors that were not predictable from the prior art references cited by the Examiner, whether considered alone or in the aggregate. The results discussed in the previously filed Rule 132 declarations are unexpected in that human cells appear to have reduced innate immunity against Ad28 as compared to Ad5, which enhances the therapeutic efficacy of Ad28 vectors in inner ear cells (See page 5 of Applicant remarks filed on 06/24/2010).

In response, Applicant's arguments filed on 06/24/2010 totally ignore the teachings of Bout et al. (US patent 6,913,922, issued on 07/05/2005), which is one of the two references (i.e. Bout et al. and Wigand et al.) specifically cited to address the limitation regarding Ad28 in the Final office action mailed on 03/24/2010.

For the clarity of record, the statements documented on pages 9-10 of Final office action mailed on 03/24/2010 are reiterated below.

Related to the teachings by Falck-Pedersen et al., Bout et al. teaches that Adenovirus serotypes differ in their natural tropism. The adenovirus serotypes 2 and 5 (serotype subgroup C), serotype 4 (subgroup E) and serotype 7 (subgroup B) all have a natural affiliation towards lung epithelia and other respiratory tissues. In contrast, serotypes 40 and 41 (subgroup F) have a natural affiliation towards the gastrointestinal tract. The serotypes described, differ in at least capsid proteins (penton-base, hexon), proteins responsible for cell binding (fiber protein), and proteins involved in adenovirus replication. This difference in tropism and capsid protein among serotypes has led to the many research efforts aimed at redirecting the adenovirus tropism by modification of the capsid proteins (See abstract, Bout et al., 2005).

It is worth noting that Bout et al. clearly indicates that adenovirus serotypes 2 and 5 (serotype subgroup C), serotype 4 (subgroup E), serotype 7 (subgroup B), and serotypes 40 and 41 (subgroup F) all have a natural affiliation, which is not the cells of inner cells recited in claim 35 of instant application. Therefore, a skilled artisan would not have considered the use of the adenoviral vector belonging to subgroup B, C, E, or F for delivery of gene to cells of inner ears as an optimal choice for the claimed methods based on the combined teachings of Falck-Pedersen et al. and Bout et al. It is further noted there are definitive number (i.e. three) of species of adenoviral vector belong to Group A (See Table shown between columns 1-2, provided above in this rejection, Falck-Pedersen et al.); and with regard to Group D adenoviral vectors, Falck-Pedersen et al. specifically teaches serotypes Ad30 and Ad36 as preferred adenoviruses of Group D adenoviral vectors (See lines 2-3, column 8, Falck-Pedersen et al.).

Relevant to the relationship between Ad28 recited in claim 35 and preferred Ad36 taught by Falck-Pedersen et al., Wigand et al. teaches that from the DNA restriction analysis, the DNA structure of Ad36 (which is a preferred adenovirus taught by Falck-Pedersen et al.) is closely related to Ad28 (see Fig. 4, Wigand et al., 1980) and is also similar to other subgroup D adenoviruses. As a consequence of the high degree of DNA/DNA homology between adenovirus types belonging to the same subgroups also DNA restriction patterns of subgroup members should be expected to display similarities (See Discussion, page 232, Wigand et al., 1980).

Furthermore, Falck-Pedersen et al. specifically teaches that any subtype, mixture of subtypes, or chimeric adenovirus can be used as the source of nucleic acid for the generation of the adenoviral vectors, and furthermore selecting a species of adenoviral vector from a given subgroup adenoviral vector is considered as a routine optimization for desired viral tropism well known for a skilled artisan in gene therapy, which is evident by the teachings of Bout et al. (2005).

Furthermore, as documented on page 12 of Final office action mailed on 03/24/2010, it would have been obvious to one of ordinary skill in the art to combine the method of generating hair cells by delivering nucleic acid encoding an atonal associated factor to the inner ear of a subject as taught by Zoghbi et al. using Ad28 which is closely related to the preferred Ad36 adenoviral vector belonging to subgroup D to circumvent host immunity taught by the combined teachings of Falck-Pedersen et al., Bout et al., and Wigand et al. because (i) the presence of immune response to subgroup C adenovirus prevent efficacious adenovirus vector administration in vivo, and Ad36 being a preferred vector of Group D adenoviral vectors, by the teachings of Falck-Pedersen et al., and (ii) adenovirus serotypes 2 and 5 (serotype subgroup C), serotype 4 (subgroup E), serotype 7 (subgroup B), and serotypes 40 and 41 (subgroup F) all have a natural affiliation, which is not the cells of inner cells recited in claim 35 of instant application, by the teachings of Bout et al., and (iii) Ad28 is a close species to Ad36 among Group D adenoviral vectors, by the teachings of Wigand et al.

As such, the ordinary artisan would have been motivated to use the serotype Ad28 adenoviral vector belonging to subgroup D as a preferred adenoviral vector to deliver nucleic acid sequence encoding Hath1 in vivo because its effectiveness in expressing the gene of interest in vivo without provoking undesired host immunity to the adenoviral vector.

The level of skill in art of molecular cloning is high. Absent evidence from the contrary, one of ordinary skill in the art would have reasonable expectation of success to replace the native coat protein with a natural or engineered coat protein in an Ad28 belonging to adenoviral vector of subgroup D and deliver it to inner ear to generate sensory hair cells.

Therefore, the claimed invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Finally, it is worth noting that the claimed methods do not require any active step pertaining to "a non-subgroup C vector to transduce inner ear cells more efficiently than subgroup C vectors" as Applicant had argued and stated in the declaration filed on 12/17/2009. The references cited in the maintained 103 rejections are not required to disclose the motivation identical to Applicant's motivation for choosing Ad28 (serotype D) as the vector used in the claimed methods. In this regard, it is emphasized again that Falck-Pedersen et al. specifically discloses the limitations on the use of group C adenoviral gene therapy vectors because a host can develop an immune response to the particular adenoviral vector being used in gene therapy as a result of natural exposure of the host to the same type of adenovirus prior to the initiation of gene therapy or as a result of the exposure of the host to the adenoviral vector in the course of the gene therapy itself (See lines 34-40 column 6, Falck-Pedersen et al.). Furthermore, Bout et al. clearly indicates that adenovirus serotypes 2 and 5 (serotype subgroup C), serotype 4 (subgroup E), serotype 7 (subgroup B), and serotypes 40 and 41 (subgroup F) all have a natural affiliation, which is not the cells of inner cells recited in claim 35 of instant application. Therefore, a skilled artisan would not have considered the use of the adenoviral vector belonging to subgroup B, C, E, or F for delivery of gene to cells of inner ears as an optimal choice for the claimed methods based on the combined teachings of Falck-Pedersen et al. and Bout et al. It is further noted there are definitive number (i.e. three) of species of adenoviral vector belong to Group A (See Table shown between columns 1-2, Falck-Pedersen et al.); and with regard to Group D adenoviral vectors, Falck-Pedersen et al. specifically teaches serotypes Ad30 and Ad36 as preferred adenoviruses of Group D adenoviral vectors (See lines 2-3, column 8, Falck-Pedersen et al.). Relevant to the relationship between Ad28 recited in claim 35 and preferred Ad36 taught by Falck-Pedersen et al., Wigand et al. teaches that from the DNA restriction analysis, the DNA structure of Ad36 (which is a preferred adenovirus taught by Falck-Pedersen et al.) is closely related to Ad28 (see Fig. 4, Wigand et al., 1980).

/Wu-Cheng Winston Shen/
Primary Examiner, Art Unit 1632